Human life has always entailed exposure to chemicals. We cannot deny the fact that the development of new drugs in the 20th century has dramatically changed the public health care and has considerably increased the average life expectancy. At the same time, drugs have their own side effects which may also include genotoxicity. The protection of the human gene pool and the integral relationship between mutagenicity and carcinogenicity are the two major factors which imparts vital importance to genotoxicity testing of chemicals of potential human exposure. Another important factor in assessing the consequences of genetic effects is the location of the affected cell. Because, if mutations occur in the somatic cells, the resultant effect is only on the individual exposed to the genotoxic agent; however, if alteration occurs in gametes (sperm or ova) the change may affect subsequent generations.

In most of the developing countries including that of India, with generally poor economic conditions of the population, have few trained medical personnel.
Therefore, all medical ailments are not brought under direct medical supervision. As a result, a large percentage of the population resorts to self-medication with complete ignorance of the correct prescriptions. Further, the drugs are not strictly obtainable by prescriptions, but are readily available as over the counter products for the general public which pose an added threat of indiscriminate use and abuse.

Recently, there is a growing concern about possible genotoxic and mutagenic potential of marketed pharmaceuticals in mammalian cells. Adequate \textit{in vivo} cytogenetic data are not available for many of the pharmaceuticals. Therefore, it is imperative that detailed investigations are carried out on the genotoxicity of marketed pharmaceuticals using multiple cytogenetic endpoints in multiple laboratories in a global basis. This will help formulation of regulatory policy guidelines as to ensure better public health, which is the ultimate objective of drug development.

There is significant numbers of pharmaceuticals for which genotoxicity data on \textit{in vivo} mammalian cytogenetic assays is not at all available. In addition, considerable controversies exist among the genotoxicity reports arising out of different laboratories. Consequently, adequate \textit{in vivo} cytogenetic data are not available for many of the pharmaceuticals.

In the present study, devoted to the same objective, the cytogenetic effects of six commonly used marketed pharmaceuticals namely metronidazole,
ciprofloxacin, chloroquine, acetaminophen, nimesulide and aspirin were investigated in Swiss albino mice in vivo test system using various cytogenetic end points like bone marrow chromosome aberration and micro nucleus assay, and sperm head shape abnormality assay. Further, the pharmaceutical agents may hyper sensitize the cells to another mutagen by way of altering its physiology even though it itself does not directly interact with the cellular DNA. Therefore, considering the above facts and in the light of the available literature, the present studies were undertaken with the following objectives:

- To study the genotoxic effects of some commonly prescribed marketed pharmaceuticals in the somatic cells of mammalian test systems in vivo.
- To evaluate the effects of these pharmaceuticals in the male germ line cells.
- To study the drug – mutagen interactions so as to evaluate the acquired susceptibility using the combined treatment with known mutagen.
- To explore the possibility of using vitamin C to reduce drug – induced mutagenicity.

The major findings of the present study are summarized as under:

1. Four of the six pharmaceuticals namely metronidazole, ciprofloxacin, chloroquine and acetaminophen induced significant increase in the frequency of chromosome aberrations in the bone marrow cells of mice.
2. Following the treatment of the test chemicals, significantly higher frequencies of chromatid and isochromatid type of gaps were observed as compared to the untreated control, suggesting in favour of the hypothesis that gaps arise as a consequence of exposure to genotoxic agents and are not artifacts.

3. In the dose ranges tested, three of the six pharmaceuticals analyzed in the present study, namely metronidazole, ciprofloxacin and chloroquine induced significant increase in the frequency of micronucleated cells in the bone marrow cells of mice.

4. The comparison between the frequency of chromosome aberrations and micronucleated bone marrow cells revealed that the frequency of the latter was significantly lower for all the six pharmaceuticals tested. Since all the broken fragments do not form visible micronucleus, and highly damaged cells may not become able to complete the cell division process, the present observations were as anticipated. This may further indicate towards a clastogenic rather than aneugenic effect induced by the test chemicals.

5. In the sperm abnormality assay, in contrast to chromosome aberration and micronucleus analysis, all the six pharmaceuticals induced significant increase in the frequency of sperm head abnormality following 21 days of the treatment. These findings indicate that the germ cells may be more
sensitive as compared to the somatic cells so far as genotoxicity is concerned.

6. The present findings supports earlier hypothesis that toxicology studies, in themselves, are quite complex with sources of variability may result from the dose and delivery of the chemical under study, the choice of animal species, and the differences in biological and pathological responses of various tissues. The present findings suggest differential sensitivity of somatic and germ cells to nimesulide and aspirin.

7. Except for acetaminophen, all the other five pharmaceuticals induced significant increase in the frequency of sperm head abnormality following 24h of the treatment. The observed abnormalities in the sperm head morphology at 24h of the treatment may not be attributable to genetic effects. Therefore, it is possible that in the short term, the said pharmaceuticals may interact with the cell membrane components thus resulting in the morphological alterations.

8. Chloroquine induced very high frequency of sperm head abnormalities at 24h of the treatment as compared to the other pharmaceuticals tested. However, vitamin C pretreatment could reduce the effect by about 65 – 70%.

9. Pretreatment with vitamin C significantly reduced the genotoxic effects of observed in the present study. However, it did not show complete protection indicating that the same can be used to a limited extent in
protecting the cells from genotoxicity induced by the pharmaceuticals in the dose ranges tested.

10. Combined treatment with radiation showed significant increase in the frequency of chromosome aberrations. It has been found that in general, when radiation exposure is given following the treatment of the test agent, the effects are more pronounced than in the animals receiving the radiation exposure prior to the treatment of the test agent.

11. The results of the present study indicate that aspirin and nimesulide may be considered to be safe drugs for somatic cells so far as genotoxic potential is concerned. However, further studies are required on their mutagenic potential in germ line cells.

12. Apart from earlier reports, the present study provides further evidence in support of earlier findings that aspirin may sensitize the cells to radiation damage.

13. The two test parameters such as structural chromosome aberrations and bone marrow micronucleus taken together revealed that the six pharmaceuticals, in the present experimental condition and dose ranges studied, in decreasing order of their genotoxic potential are metronidazole > ciprofloxacin > chloroquine > acetaminophen > nimesulide > aspirin.
14. The present findings provide further evidence that genotoxicity testing using multiple cytogenetic end points marginally clarify the true potential of a genotoxic agent, which is otherwise not possible in test models that use single end points for hazard assessment.

Based on the above findings, it can be concluded that metronidazole, ciprofloxacin and chloroquine may cause significant genetic hazards to the exposed population and hence exposure to these chemicals should be restricted. The relative safety of, the otherwise considered to be safe, drugs nimesulide and aspirin is doubtful so far as their mutagenic potential in the male germ line cells is concerned. Vitamin C pretreatment may reduce the genotoxic effects of the tested pharmaceuticals to a limited extent. Since most of the tested pharmaceuticals showed synergistic effects when treated with radiation, exposure to even low levels of radiation during medication should be avoided. Further, the health risks are sufficient to require the continuous testing of these pharmaceuticals using specific genetic locus to make certain that the public health is protected.